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Pharmacology of the GABAergic system: Effects of progabide, a GABA receptor agonist^{*1}

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Abstract

Stimulation of GABA receptors (e.g. by progabide, a new GABA receptor antagonist, or by muscimol) enhances the liberation of norepinephrine in limbic forebrain areas of the rat and reduces 5-hydroxytryptamine turnover. On repeated administration, this latter effect is associated with an up-regulation of 5-HT₂ receptors as it occurs after electroconvulsive shock. The monoaminergic changes induced by progabide, though dissimilar from those induced by tricyclics, are probably connected with the antidepressant action of the compound observed in double-blind clinical trials.

In the basal ganglia, GABA receptor agonists reduce dopamine turnover and potentiate the cataleptogenic action of neuroleptics. They also antagonize the stereotypic behaviour induced by dopaminomimetics, indicating an additional action beyond the dopamine synapse. On repeated co-administration with neuroleptics, progabide antagonizes the tolerance to the cataleptogenic action, the supersensitivity to dopaminomimetics, and the increase in ³H-spiperone binding which are caused by sustained neuroleptic treatment. This appears to be the basis for the clinical action of progabide in neuroleptic-induced dyskinesia, L-dopa-induced involuntary movements, and possibly mania.

GABA receptor agonists decrease cellular excitability in several animal models and antagonize seizures, whatever their origin (GABA-mediated or GABA unrelated mechanisms). Progabide has been shown to be effective in various forms of epilepsy in double-blind and long-term clinical trials. The compound exerts a therapeutic action in patients resistant to "classical" antiepileptic drugs, in the virtual absence of major side effects.

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*1 Presented in part at the XIV International Congress of the International Society of Psychoneuroendocrinology, New York City, 12–16 June 1983.

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GAMMA aminobutyric acid (GABA), a modulator of anterior pituitary hormone secretion by hypothalamic and pituitary action^{*1}

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Abstract

We have evaluated the role of GABA in the control of anterior pituitary (AP) hormone secretion by injecting it into the third ventricle of ovariectomized, ovariectomized-steroid primed and male rats. Specificity of the effects was determined by injecting the GABA blocker, bicuculline. The action of GABA directly on the pituitary was evaluated *in vitro*. The results indicate that intraventricular GABA can stimulate LH, growth hormone (GH) and, at high doses, prolactin (Prl) release, whereas low doses inhibit Prl and all doses inhibit TSH release. All of these actions are blocked by bicuculline. Intraventricular GABA administration is followed by an elevation of hypothalamic norepinephrine (NE) and median eminence dopamine (DA) levels and AP DA levels, which indicates that the compound stimulates both NE and DA release. The actions on GH and LH appear to proceed independently of DA, since the DA receptor blocker, pimozide, did not interfere with these effects, whereas the action to elevate Prl and to lower TSH was blocked by DA receptor blockade. Anterior pituitary hormone release by AP's incubated with GABA *in vitro* was unaltered except for an inhibition of Prl release by very high GABA doses, which could be blocked by bicuculline. Intravenous injection of bicuculline to assess the physiological significance of GABA in control of AP hormone secretion revealed no effect on FSH but a delayed rise in LH, an initial rise in Prl, followed by a fall, a tendency for GH values to rise and a dramatic fall in TSH levels. These results suggest the possibility that GABA plays a physiological role in the control of AP hormone secretion, mainly via a hypothalamic action.

^{*1} Presented in part at the XIV International Congress of the International Society of Psychoneuroendocrinology, New York City, 12–16 June 1983.

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Bartholini, G., *Psychoneuroendocrinology*, Jan 1984
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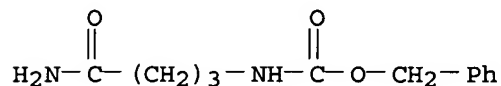
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10/049328

L1 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 35821-20-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN Carbamic acid, (4-amino-4-oxobutyl)-, phenylmethyl ester (9CI) (CA INDEX NAME)

OTHER NAMES:

CN **N-(Benzoxycarbonyl)-γ-aminobutyramide**
CN N-Benzylloxycarbonyl-γ-aminobutyric acid amide
FS 3D CONCORD
MF C12 H16 N2 O3
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



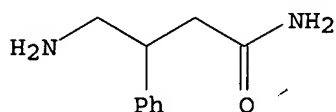
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9 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 25271-48-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Hydrocinnamamide, β-(aminomethyl)-, dihydrochloride, DL- (8CI) (CA INDEX NAME)

OTHER NAMES:

CN **DL-β-Phenyl-γ-aminobutyramide dihydrochloride**
MF C10 H14 N2 O . 2 Cl H
LC STN Files: CA, CAPLUS, TOXCENTER
CRN (102571-00-6)



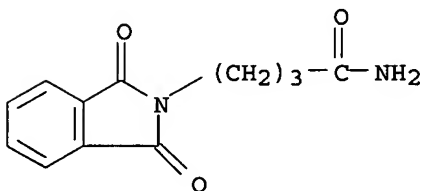
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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN 3459-33-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2H-Isoindole-2-butanamide, 1,3-dihydro-1,3-dioxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Isoindolinebutyramide, 1,3-dioxo- (7CI, 8CI)
OTHER NAMES:
CN 4-Phthalimidobutyramide

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CN N-Phthalyl- γ -aminobutyramide
FS 3D CONCORD
MF C12 H12 N2 O3
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, RTECS*, TOXCENTER,
USPAT2, USPATFULL
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14 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s GABA/cn
L2 1 GABA/CN

=> d 12

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 56-12-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butyric acid, 4-amino- (7CI, 8CI)
OTHER NAMES:
CN γ -Aminobutanoic acid
CN γ -Aminobutryic acid
CN γ -Aminobutyric acid
CN ω -Aminobutyric acid
CN 3-Carboxypropylamine
CN 4-Aminobutanoic acid
CN 4-Aminobutyric acid
CN Aminalon
CN GABA
CN Gaballon
CN Gamarex
CN Gammalon
CN Gammalone
CN Gammar
CN Gammasol
CN Mielogen
CN Mielomade
CN NSC 27418
CN NSC 32044
CN NSC 45460
CN NSC 51295

Jagoe

10/049328

CN Pharmagaba
CN Pharmagaba 20
CN Pharmagaba 20D
CN Piperidic acid
CN Piperidinic acid
FS 3D CONCORD
DR 3131-86-0
MF C4 H9 N O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO,
CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX,
CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB,
IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PROMT, PS,
RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL,
VETU
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28475 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN

RN 56-12-2 REGISTRY

CN Butanoic acid, 4-amino- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Butyric acid, 4-amino- (7CI, 8CI)

OTHER NAMES:

CN γ -Aminobutanoic acid; γ -Aminobutyric acid;
 γ -Aminobutyric acid; ω -Aminobutyric acid;
3-Carboxypropylamine; 4-Aminobutanoic acid; 4-Aminobutyric acid;
Aminalon; GABA; Gaballon; Gamarex; Gammalon; Gammalone; Gammar;
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51295; Pharmagaba; Pharmagaba 20; Pharmagaba 20D; Piperidic acid;
Piperidinic acid